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Date:	July 13, 2003	Fr m:	John A. Sopp
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Re:	U.S. Patent Application No. 09/654,227 Our Ref (Atmy Docket): Plovin-1A		
Total No of Pages: 8 ; if you do not receive all pages, please call 703-243-6333			

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- PLEASE DELIVER DIRECTLY TO MS. BAHAR, ART UNIT 1617 -

Dear Ms. Bahar:

Following my phone call of earlier today, attached is a Declaration I referred to for your review in connection with the Interview scheduled for Monday, July 14.

Very truly yours,

John A. Sopp

-Please note, the declaration was filed in a related application but should equally apply here.

JAS

For The Unit d States Patent and Trademark Office

Applicants:	Heil et al.
Application no.:	09/757,688
National Filing Date:	11 January 2001
Title:	Drospirenone for Hormone Replacement Therapy
Examiner:	Laksmi S Channavajjala
Art unit:	1615

DECLARATION OF ELLIESEN

1. I, Jörg Elliesen of Berlin, Germany, one of the named inventors of the patent US 5,922,349 do state and declare as follows:

2. I believe that I am the person skilled in the art to which the above-captioned application pertains. Please find attached to this declaration my Curricula Vitae.

3. I have read and understood the pending claims in the application in question as well as the Office Action related thereto, dated 24 October 2001, in which US 5,922,349 was first cited against the application in question. I have also read and understood the communication, dated 28 May 2002, which was filed in response to this Office Action. In respect to the Office Action, dated 26 June 2002, in which the corresponding PCT application to US 5,922,349 is cited (WO 97/11680), I have the following comments:

4. The objective of US 5,922,349 (WO 97/11680) relates to a device containing a pharmaceutical composition comprising an estrogen and a progestin formulated for topical delivery of variable doses such as compositions in the form of extrudable semi-solids, viscous liquids or spreadable sticks. Such compositions are of importance in the managing of HRT or contraception wherein it may be desirable to adjust the effective dose on an individual basis.

5. I respectfully submit that according to the present invention, the progestins applicable for use in the questioned device relate to natural as well as synthetic progestins which are known to give a clinical relevant response. Of relevance are the synthetic progestins, norethisterone and its ester; norgestrel; levo-norgestrel; chlormadinone acetate; cyproterone acetate; desogestrel; 3-ketodesogestrel; drospirenone; norgestimate or gestodene can be used in such a device. Progesterone is a natural hormone, but natural occurring progesterone has rarely been used in clinical practice because of rapid hepatic

metabolism and poor bioavailability (see Appendix A, item 3). At the time the invention was made it was generally known that synthetic progestins could be used in oral contraceptive preparations and to treat menopausal symptoms. However, progesterone has not been used because of the above-mentioned problems.

6. It has been known in the art that progesterone should be formulated in a particular manner in order to achieve a clinical relevant response upon administering progesterone orally. For example, it was known that the bioavailability of progesterone could be improved upon suspending progesterone in a fatty acid, reducing the particle size of progesterone, or by combining the techniques of reducing the particle size and suspending in fatty acids (see Appendix A, item 1 to 3 and 5). However, even after micronization of progesterone, the absolute bioavailability upon oral administration is only in the order of 6-8% (Lingniere, page 43, column 1). Therefore, rather high doses of micronized progesterone are needed in order to achieve a clinical relevant response such as between 100 and 300 mg.

7. It was further known that upon administering micronized progesterone by non-parenteral routes such as by the sublingual, the vaginal or the rectal route the bioavailability of progesterone was shown to be better than by the oral route (see Appendix A, item 4).

8. I believe that the phrase "micronized progesterone" has been a standard phrase in the art in that it was the clear understanding that progesterone need to be provided in micronized form in order to be clinical relevant. As stated, natural progesterone has no clinical relevance.

9. Thus, since it was known in the art that progesterone needed to be provided in micronized form, I indicated this in our patent application (WO 97/11680) by preceding the word "progesterone" by the term "micronized" so as to use the standard phrase in the art.

10. Accordingly, it was not our intention to mention that other progestins should be applied in micronized form.

11. I acknowledge that a reader of column 10, lines 16-28 of US 5,922,349 may have the impression that all the progestins mentioned, is in micronized form. Furthermore, I acknowledge that it also may be the impression from WO 97/11680, page 15, lines 8-18 that all mentioned progestins are in micronized form. In particular, I believe that a person, who is not skilled in the art in which the invention pertain, but are skilled in English language, may get the impression that all progestins is in micronized form. However, I firmly believe that a person skilled in the art, which may know of the particular poor

bioavailability of progesterone and of the standard phrase "micronized progesterone" will understand that that only progesterone is meant to be in micronized form.

12. In summary, I would like to note that it was only my intention to mention that progesterone is in micronized form and not to remark that all progestins should be applied in micronized form. The overall reason is summarised below:
    - it was known that natural progesterone did not give a clinical relevant response because of poor bioavailability and that progesterone need to being provided in micronized form to give a clinical relevant response.
    - it was known that synthetic progestins, which are not metabolised so extensively in vivo as natural progesterone, resulted in clinical relevant response upon being administered orally.
    - it was known that upon administration of progesterone in micronized form by non-parenteral routes, the bioavailability was better than for the oral route. Thus, I were motivated to claim that for topical administration, the progesterone should be applied in micronized form.

11. For the reasons stated above, I am of the opinion that micronized drospirenone are not cited in US 5,922,349 or in WO 97/11680.

12. I further declare that all statements made herein of our knowledge are true, and further that the statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issued thereon.

Dated: 15. Jan. 2003 Signature: _____

Jörg Elliesen

Appendix A

Examples, wherein it is stated that progesterone, but not synthetic progestins need to be formulated properly, for example by micronization, in order to achieve a clinical relevant response:

1. Kincl F. A. et al. Increasing oral bioavailability of progesterone by formulation. J, Steroid Biochem, vol. 9, pp 83-84, 1978.
   Kincl et al teaches:
- progesterone is metabolised in the small intestine and there is considerable enterohepatic recirculation of progesterone metabolites, thus leading to poor bioavailability of progesterone.
- Poor bioavailability of progesterone can be partially overcome by an addition of a cholesterol ester. Kincl also suggest that micronization of progesterone may increase bioavailability.

2. Whitehead M. I. Absorption and metabolism of oral progesterone. Br. Med. Journal, 22 March, pp 825-827, 1980.

   Whitehead et al teach:
   - naturally occurring progesterone has rarely been used in clinical practice due to low absorption rate and high clearance from the blood system. Only 25 % of the administered progesterone reach the peripheral blood system.
   - synthetic progestins have been use with benefit, but may suffer from adverse reactions due to their androgenic or oestrogenic activity.
   - administering progesterone either twice daily or in combination with cholesterole pivalate, which increases the bioavailability will produce this effect.

3. Maxson and Hargrove. Bioavailability of oral micronized progesterone. Fertility and Sterility, vol 44, No 5, pp 622-626, 1985.

   Maxson and Hargrove teach:
   - progesterone has not been administered orally because of reportedly poor gastrointestinal absorption and a short biological half-life.
   - the synthetic derivatives, although orally active, have a number of disadvantages and fail to mimic natural progesterone completely.
   - Unfortunately, the oral route of administration of naturally occurring progesterone has not been practical because of the rapid hepatic metabolism and the poor bioavailability

of this steroid. Thus, synthetic derivatives have been the only orally active progestional agents available.

- synthetic progestins suffer from a number of disadvantages. None of these agents have effects identical to natural progesterone and some exhibit prominent side effects.
- reduction in the particle size of progesterone by micronization permits increases aqueous dissolution in the intestine and increases plasma concentration of progesterone in male rats.
- micronized form of natural progesterone is readily absorbed orally and may offer a novel alternative to the synthetic agents.

4. Chakmakjian and Zachariah. Bioavailability of progesterone with different modes of administration. Journal of reproductive medicine, vol 32, No 6, pp 443-448, 1987.

Chakmakjian and Zachariah teach:

- Oral progesterone administration could become an attractive alternative to the currently used oral mode of administering synthetic progestins. Its clinical usefulness in the past was limited because of its extensive degradation following ingestion. Therefore, orally effective, synthetic progestional agents have been substituted in the management of for example HRT.
- micronized drospirenone may be administered sublingually, orally, vaginally or by the rectal route. The bioavailability following rectal administration is significant higher than the bioavailability following the other routes. The oral bioavailability is significant lower than the other routes.

5. Hargrove J. T. et al. Absorption of oral progesterone is influenced by vehicle and particle size. A. J Obstet Gynecol, p 948-951, 1989.

- Hargrove et al teaches:
- no significant difference is found for either peak concentration, time to peak, or mean area under the curve upon admin:stering preparations made by plain-milled progesterone or micronized progesterone.
- upon administering micronized progesterone in a oil, the peak concentration was significant higher and the time to peak significant lower than for other preparations (preparations with micronized or plain-milled progesterone or preparations comprising plain-milled progesterone and an oil. This clearly indicates a synergistic effect of the two processes (micronization and oil).

- of particular interest was the observation that the suspension of non-micronized progesterone in oil did not significantly enhance circulating progesterone concentrations over either micronized or plain-milled progesterone.
- the optimal preparation of progesterone for the administration of progesterone should include micronization of the progesterone particles and dissolution in oils.

CURRICULUM VITAE

Name:	Dr. med. Jörg Elliesen
Born:	July 7, 1959
Nationality:	German

Education and Qualifications

1969-1978	Secondary education (Droste-Hülshoff Gymnasium, Freiburg)
1978	Secondary school completion examination (Abitur)
1979-1985	Medical School, Free University of Berlin
1985	Approbation as physician
1993	Doctoral thesis (MD), Free University of Berlin

Employments

1986	Internship in internal medicine (Rudolph-Virchow Krankenhaus)
1987	Clinical Research and Development (Hormone Therapy), Schering AG Berlin
1996-1999	Medical & Scientific Affairs, Schering AG, Expert Position for Clinical Research
2000-2001	Clinical Development Andrology Jenapharm GmbH & Co. KG, Jena
2001-present	Corporate Clinical Development – Male FC/HT Schering AG, Berlin